# Edoxaban tosylate (Savaysa™) New Drug Update

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| ***Drug Name:*** | **edoxaban tosylate** |
| ***Trade Name (Manufacturer):*** | **Savaysa (Daiichi-Sankyo)** |
| ***Form:*** | Tablet |
| ***Strength:*** | 15 mg, 30 mg, 60 mg |
| ***FDA Approval:*** | January 8, 2015 |
| ***Market Availability:*** | Available |
| ***FDA Approval Classification:*** | Standard Review |
| ***Classification:*** | Specific Therapeutic Class (HIC3): Direct factor Xa inhibitors (M9V) |

## INDICATION[1]

Edoxaban (Savaysa), an oral direct factor Xa inhibitor, is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF). In patients with NVAF, edoxaban should not be used in patients with a creatinine clearance (CrCl) > 95 mL/min due to an increased risk of ischemic stroke compared to warfarin.

Edoxaban is also indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following five to ten days of initial therapy with a parenteral anticoagulant.

## CONTRAINDICATIONS/WARNINGS

Edoxaban is contraindicated in patients with active pathological bleeding. There is an increased risk of bleeding with edoxaban. Concomitant use of other drugs affecting hemostasis such as aspirin, other antiplatelet agents, fibrinolytics, other anti-thrombotic agents or chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk of bleeding.

Patients receiving neuraxial anesthesia or undergoing a spinal/epidural puncture who are receiving edoxaban are at an increased risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis. Indwelling epidural or intrathecal catheters should not be removed earlier than 12 hours after the last administration of edoxaban and the next dose of edoxaban should not be administered earlier than two hours after the removal of the catheter.

There is an increased risk of stroke associated with discontinuation of edoxaban in patients with NVAF, if no alternative anticoagulation is provided. Edoxaban should not be used in patients with CrCl > 95 mL/min due to an increased rate of ischemic stroke in patients receiving edoxaban 60 mg daily

compared to warfarin. The safety and efficacy of edoxaban has not been studied in patients with mechanical heart valves or moderate to severe mitral stenosis and the use of edoxaban in these patients is not recommended.

There is no established reversal agent for the anticoagulant effects of edoxaban which can be expected to persist for approximately 24 hours after the last dose.

## DRUG INTERACTIONS

Edoxaban is a substrate of the P-gp transporter.

The concomitant use of edoxaban with rifampin (a P-gp inducer) should be avoided.

There are no dose alterations recommended in NVAF patients receiving concomitant P-gp inhibitors (e.g. ketoconazole, verapamil, erythromycin, cyclosporine, amiodarone). However, based on the Hokusai VTE study, patients receiving edoxaban for the treatment of DVT and/or PE should have their dose reduced to edoxaban 30 mg once daily if they are receiving specific concomitant P-gp inhibitors (verapamil and quinidine or the short-term concomitant administration of azithromycin, clarithromycin, erythromycin, oral itraconazole or oral ketoconazole).

Co-administration of anticoagulants, antiplatelet drugs and thrombolytics may increase the risk of bleeding. Patients who require chronic treatment with low dose aspirin or NSAIDs should be monitored carefully for signs or symptoms of bleeding or blood loss. Long-term concomitant treatment with edoxaban and other anticoagulants is not recommended due to an increased risk of bleeding; however short-term co-administration may be needed for patients transitioning to or from edoxaban.

## COMMON ADVERSE EFFECTS

The most common adverse reactions to edoxaban are bleeding, anemia, rash and abnormal liver function tests. In the NVAF trial, bleeding led to discontinuation of edoxaban in 3.9 percent of cases; this was lower than the 4.1 percent discontinuation rate due to bleeding incidence with warfarin. The most common site of major bleeding with edoxaban was the gastrointestinal (GI) tract. In patients with DVT and/or PE treated with edoxaban, the incidence of clinically relevant bleeding was lower with edoxaban compared to warfarin (HR: 0.81 (95% CI: 0.71-0.94, p=0.004).

Edoxaban should be discontinued at least 24 hours before invasive or surgical procedures because of the risk of bleeding. Edoxaban can be restarted after the procedure as soon as adequate hemostasis has been established.

## SPECIAL POPULATIONS

### Pregnancy

Pregnancy Category C.

### Pediatrics

The safety and effectiveness of edoxaban in pediatric patients has not been established.

### Geriatrics

In both the NVAF trial as well as the DVT/PE treatment trials, the efficacy and safety of edoxaban in elderly (65 years or older) and younger patients were similar.

### Hepatic Impairment

The use of edoxaban in patients with moderate or severe hepatic impairment (Child-Pugh B and C) is not recommended as these patients may have intrinsic coagulation abnormalities. No dose reduction is required in patients with mild hepatic impairment (Child-Pugh A).

### Renal Impairment

Renal clearance accounts for approximately 50 percent of the total clearance of edoxaban and therefore reduced renal function leads to higher blood concentrations of edoxaban. The dose of edoxaban should be reduced to 30 mg once daily in patients with CrCL 15-50 mL/min. The use of edoxaban in patients with CrCL < 15 mL is not recommended due to lack of data in this patient population.

### Body Weight

The dose of edoxaban should be reduced to 30 mg daily in patients with body weight less than or equal to 60 kg who are being treated for VTE based on data from the Hokusai-VTE trial.

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## DOSAGES

In the treatment of patients with NVAF, creatinine clearance should be assessed prior to initiating therapy. The recommended dose is edoxaban 60 mg once daily in patients with CrCL > 50 mL/min to ≤95 mL/min. Edoxaban should not be used in patients with a CrCL > 95 mL/min and should be reduced to 30 mg once daily in patients with CrCL 15 mL/min to 50 mL/min.

The recommended dose for the treatment of DVT and/or PE is 60 mg once daily. The recommended dose is 30 mg once daily for patients with CrCL 15 to 50 mL/min or those with a body weight ≤ 60 kg or patients who are taking certain P-gp inhibitors (verapamil, quinidine or the short-term concomitant administration of azithromycin, clarithromycin, erythromycin, or itraconazole or oral ketoconazole).

Recommendations for transitioning to or from edoxaban with either parenteral anticoagulants or other oral anticoagulants are provided in the labeling.

## CLINICAL TRIALS

*A literature search was conducted using "edoxaban"*

**ENGAGE AF-TIMI 48** was a randomized, double-blind, double dummy trial comparing two doses of edoxaban (30 mg or 60 mg) or warfarin (dose adjusted to achieve an international normalized ratio [INR] of 2.0 to 3.0) in patients with atrial fibrillation who were at moderate to high risk for stroke.[2] This

international trial was conducted in 46 countries and randomized 21,105 patients who were followed for a median of 2.8 years. Enrolled patients had either experienced a prior stroke (ischemic or unknown type), transient ischemic attack (TIA) or a non-CNS embolism or they had two or more of the following risk factors: age ≥ 75 years, hypertension, heart failure or diabetes. The primary efficacy end point was the time to first occurrence of stroke or other systemic embolic event. The secondary endpoint was ischemic stroke, hemorrhagic stroke, systemic embolism and a composite of deaths due to cardiovascular causes. The principal safety endpoint was major bleeding during treatment. During the treatment period, a stroke or systemic embolic event occurred in232 patients in the warfarin group (representing a rate of 1.5 percent per year) as compared with 182 patients in the edoxaban 60 mg/day group (a rate of 1.18 percent per year; hazard ratio versus warfarin, 0.79, 97.5 percent confidence interval [CI], 0.63 to 0.99; p<0.001 for noninferiority, p=0.02 for superiority) and 253 patients in the edoxaban 30 mg/day group (a rate of 1.61 percent per year; hazard ratio versus warfarin, 1.07; 97.5 percent confidence interval, 0.87 to 1.31; p=0.005 for noninferiority, p=0.44 for superiority). The annualized rate of hemorrhagic stroke was 0.47 percent with warfarin, as compared with 0.26 percent with edoxaban 60 mg daily (HR, 0.54; 95% CI, 0.96 to 1.34, p=0.10) and 0.16 percent with edoxaban 30 mg daily (HR, 0.33; 95% CI, 0.22 to 0.50; p<0.001). The rate of ischemic stroke was 1.25 percent with warfarin as compared with 1.25 percent with edoxaban 60 mg daily (HR, 1.00; 95 % CI, 0.83 to 1.19; p=0.97) and 1.77 percent with edoxaban 30 mg daily (HR 1.41; 95% CI, 1.19 to 1.67; p<0.001). Treatment with edoxaban was associated with lower annualized rates of death from cardiovascular causes than was warfarin: 3.17 percent with warfarin, as compared with 2.74 percent with edoxaban 60 mg daily (HR, 0.86; 95% CI, 0.77 to 0.97; p=0.01) and 2.71 percent with edoxaban 30 mg daily (HR, 0.85; 95% CI 0.76 to 0.96; p=0.008). In the safety analysis, the annualized rate of major bleeding events was 3.43% with warfarin, as compared with 2.75 % with edoxaban 60 mg daily (HR, 0.80, 95% CI, 0.71 to 0.91; p<0.001) and 1.61 percent with edoxaban 30 mg daily (HR 0.47; 95% CI, 0.41 to 0.55, p<0.001). The annualized rate of major gastrointestinal bleeding was higher with edoxaban 60 mg daily than with warfarin (1.51 percent versus 1.23 percent). A sub-group analysis revealed that in patients with CrCL > 95 mL/min the rate of ischemic stroke was higher in the edoxaban 60 mg group compared to warfarin (HR: 2.16; 95 % CI 1.17 to 3.97).

**Hokusai-VTE** was a randomized, double-blind, noninferiority study in 8,240 patients diagnosed with either DVT or PE who had initially received heparin (either low molecular weight heparin (LMWH) or unfractionated heparin (UFH).[3] Patients were randomized to edoxaban 60 mg daily or warfarin (to maintain a target INR of 2.0 to 3.0) and followed for 12 months. Patients randomized to edoxaban who had a CrCL < 50 mL/min or a body weight < 60 kg or who were receiving verapamil, quinidine or short-term concomitant therapy with azithromycin, clarithromycin, erythromycin, oral itraconazole or oral ketoconazole had their dose reduced to edoxaban 30 mg daily. The primary efficacy outcome was recurrent symptomatic venous thromboembolism (VTE) and the primary safety outcome was major or clinically relevant non-major bleeding. In the edoxaban group, 130 patients (3.2 percent) experienced a recurrent symptomatic VTE compared to 146 patients in the warfarin group (3.5 percent) (HR, 0.89; 95% CI, 0.70 to 1.13; p<0.001 for noninferiority). There were 349 (8.5 percent) patients in the edoxaban group who experienced major or clinically relevant non-major bleeding compared to 423 (10.3 percent) patients in the warfarin group (HR, 0.81; 95% CI, 0.71 to 0.94; p=0.004 for superiority).

## OTHER DRUGS USED FOR CONDITION

Oral anticoagulants with similar FDA-approved indications include warfarin, apixaban (Eliquis®), dabigatran (Pradaxa®) and rivaroxaban (Xarelto®). Similar to edoxaban, apixaban and rivaroxaban are oral direct factor Xa inhibitors while dabigatran is a direct thrombin inhibitor and warfarin is a vitamin K antagonist.

Edoxaban, rivaroxaban and warfarin are dosed once daily while apixaban and dabigatran are dosed twice daily. Warfarin requires routine INR monitoring while none of the newer oral anticoagulant agents (apixaban, dabigatran, edoxaban or rivaroxaban) currently require routine blood level monitoring.

| Drug | Reduce risk of stroke in NVAF | Prophylaxis of VTE for orthopedic surgery | Treatment of VTE | Reduce the risk of recurrence of VTE |
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| apixaban | x | x | x | x |
| dabigatran | x | | x | x |
| edoxaban | x | | x | |
| rivaroxaban | x | x | x | x |
| warfarin | x | x | x | x |

## PLACE IN THERAPY

The 2012 American College of Chest Physicians (ACCP) guidelines regarding anti-thrombotic therapy and prevention of thrombosis state that oral anticoagulation is recommended in patients with atrial fibrillation at intermediate to high risk of stroke, with dabigatran suggested over adjusted-dose vitamin K antagonist therapy. The ACCP recommendations do not yet provide any guidance on apixaban, rivaroxaban or edoxaban in the management of atrial fibrillation.[4] The 2014 American Academy of Neurology (AAN) guidelines for the prevention of stroke in nonvalvular atrial fibrillation (NVAF) conclude dabigatran 150 mg twice daily is likely more effective than warfarin with a decreased risk for intracranial hemorrhage.[5] The guidelines also conclude rivaroxaban is probably as effective as warfarin in preventing stroke or systemic embolism with a lesser frequency of intracranial hemorrhage and fatal bleeding. The AAN guidelines state apixaban 5 mg twice daily has been shown to result in a reduced mortality compared to warfarin due to a decreased risk of bleeding, including intracranial bleeding, rather than its effect on reduction of cerebral or systemic embolism compared to warfarin. The AAN guidelines do not address edoxaban.

The American College of Chest Physicians Evidence-Based Clinical Practice Guidelines for the use of Antithrombotic Therapy for VTE Disease recommend vitamin K antagonists or LMWH over dabigatran or rivaroxaban (Grade 2B) for the treatment of patients with proximal DVT or PE and do not address the use of apixaban or edoxaban.[6] The use of novel oral anticoagulants is not currently recommended for patients with malignancy and VTE because of limited data in patients with cancer.[7]

# SUGGESTED UTILIZATION MANAGEMENT

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| **Anticipated Therapeutic Class Review (TCR) Placement** | Anticoagulants |
| **Clinical Edit** | If non-preferred, trial and failure of a preferred Factor Xa inhibitor (apixaban, rivaroxaban) or dabigatran |
| **Quantity Limit** | Maximum quantity of 1 tablet/day |
| **Duration of Approval** | One year |
| **Drug to Disease Hard Edit** | No |

# REFERENCES


[1] Savaysa [package insert]. Parsippany, NJ; Daiichi Sankyo; January 2015.

[2] Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. New Engl J Med. 2013; 369:2093-2104. DOI: 10.1056/NEJMoa1310907.

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[4] You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th Edition). Chest. 2012; 141:e531S-e575S.

[5] Culebras A, Messe SR, Chaturfvedi S, et al. Summary of evidence-based guidelines update: Prevention of stroke in nonvalvular atrial fibrillation Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2014; 82:716-724 Available at: http://www.neurology.org/content/82/8/716.full.pdf. Accessed February 24, 2015.

[6] Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141(2)(Suppl):e419S-e494S Available at: http://journal.publications.chestnet.org/data/Journals/CHEST/23443/chest_141_2_suppl_e419S.pdf. Accessed February 24, 2015.

[7] Lyman GH, Bohlke K, Khorana AA, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology practice guideline update 2014. Available at: http://jco.ascopubs.org/content/early/2015/01/20/JCO.2014.59.7351.full.pdf+html Accessed February 24, 2015.